

Protocol for a Case Investigation of a Cluster of Pediatric Rhabdomyosarcoma and Pleuropulmonary Blastoma New Hampshire, 2016



Lead Agency:

Department of Health and Human Services, Division of Public Health Services, Chronic Disease Prevention and Screening Section, Cancer Prevention and Control Program

Background:

In March 2014, residents of Rye, NH, contacted the New Hampshire Department of Health and Human Services (DHHS) to report a possible cluster of rhabdomyosarcoma (RMS) among children in Rye. To determine whether the report was consistent with a cluster, DHHS followed CSTE/CDC guidance, used the New Hampshire State Cancer Registry to calculate the standardized incident ratio (SIR) for adult and pediatric cancers (any cancer type) and adult and pediatric rhabdomyosarcoma among residents living in a five-town area including and surrounding Rye, NH (1, 2). The SIRs for adult or pediatric cancers were not elevated; with the exception of the SIRs for pediatric rhabdomyosarcoma (RMS) and pediatric pleuropulmonary blastoma (PPB), consistent with a cancer cluster (2). The 2016 DHHS report concluded that a more detailed epidemiologic investigation would be unlikely to result in the identification of an environmental exposure to explain the cluster (2). However, following the release of the report a number of individuals contacted DHHS indicating potential connections to the seacoast area and children diagnosed with RMS or PPB. Additionally, in the community meeting held following the release of the report a number of people identified additional potential environmental exposures in the area (e.g., Coakley Landfill). Following these developments DHHS determined that a feasibility study to determine if there was a potential connection between cases of pediatric RMS should be conducted.

According to data from the NPCR and SEER state registries, in 2013, the rate of RMS in children ages 0-19 in the United States was 0.466 cases per 100,000 children. RMS is associated with Li-Fraumeni syndrome, neurofibromatosis 1, constitutional mismatch repair-deficiency syndrome, familial pleuropulmonary blastoma tumor predisposition and dysplasia syndrome (7, 9-11). The World Health Organization classifies RMS into embryonal, spindle cell sclerosing, alveolar, and pleomorphic subtypes. About 80% of RMS is embryonal; 15-20% of RMS is alveolar. While there are some histologic similarities between RMS and PPB, especially in early RMS and some common genetic predispositions, these are separate cancers.

Studies reported in the scientific literature have not clearly identified environmental exposures as a risk factor for RMS or PPB, but some associations have been suggested.

Given public concern over the RMS/PPB cluster, DHHS proposes performing a case investigation (case series) to interview patients or their parents/guardians in an attempt to describe patient characteristics such as demographics and clinical, family and social histories, and environmental exposures, and generate hypotheses that might explain the pediatric RMS/PPB cluster. Current hypotheses include familial/genetic factors or a common environmental exposure that might require further exploration. Case investigations involve collecting detailed information about individual patients to look for general patterns that might yield clues to a possible common explanation.

A limitation to case series investigations is that they are descriptive and primarily done to generate (but not prove) hypotheses. With the lack of a comparator group, the investigation is unable to measure the

association of exposure to outcome, does not provide information on how case-patients differ from the general population, and provides little new knowledge of environmental risk factors.

Regarding the overall approach to the pediatric RMS/PPB cluster investigation, NH DHHS has involved a variety of stakeholders, including state agencies (Department of Environmental Services), local health officials, community members, elected officials, federal agencies (Centers for Disease Control and Prevention and the Environmental Protection Agency), and academics.

Objectives:

1. To determine if a potential common cause for RMS/PPB can be identified among cases studied.
2. To inform DHHS regarding whether to recommend and to inform decisions on next steps for further investigation or monitoring.

Methods:

Steps in conducting the case investigation include: (1) creating a case definition; (2) finding and interviewing cases; and (3) analysis.

1. Case Definition

A case is defined as a case of laboratory-confirmed RMS or PPB diagnosed since 2001 in a person younger than 20 years old who spent at least 28 days (cumulative, in utero or after birth) in one of the following ten New Hampshire towns: Greenland, Hampton, Hampton Falls, New Castle, Newington, North Hampton, Portsmouth, Rye, Seabrook, or Stratham at least six months prior to diagnosis.

Laboratory-confirmed disease is defined as having a cancer-registry associated ICD-O-3 code for RMS (8900-8902, 8910, 8912, 8920, 8921) or PPB (8973), or a pathology report of RMS or PPB.

The January 2016 DHHS Report focused on the five-town area (Rye, New Castle, Portsmouth, North Hampton and Greenland). However, because of public concerns about the nuclear power plant in Seabrook, the geographic area was expanded to the ten-town area as stated above in the case definition.

Twenty-eight days of cumulative time spent in the ten-town area was a number chosen for a conservative approach. There are no clear exposures known to cause RMS or PPB, and there is also no known minimum timeframe for any possible exposure that might lead to RMS or PPB; 28 days was chosen to be more inclusive of RMS cases in our investigation. In developing this protocol, topic area experts were consulted; the consensus among the consulting experts was that a six month residency requirement was standard for use as criteria in cancer studies, so the selection of 28 days should not be interpreted as a worrisome amount of time to have been in the area but rather as an attempt to include additional cases and understand what they were doing in the ten-town area to see if their history might offer clues to an explanation.

2. Case Finding

New Hampshire Residents

Cases already known to DHHS via self-identification following release of our report will be contacted via email or phone to be consented and screened for inclusion in the case study.

The New Hampshire Cancer Registry will be used to generate a list of individuals diagnosed with RMS or PPB who were under 20 years of age at the time of diagnosis, and who were diagnosed with RMS or PPB after 2001. The parents or guardians of these individuals will be notified of our investigation through a letter from DHHS. They will be provided with a Case Definition Confirmation form to evaluate whether they meet inclusion criteria for our investigation. They will also be provided with an Informed Consent Form and the Questionnaire. If they meet the case definition, they will be asked to return all three forms to DHHS in a prepaid addressed envelope. They will be provided with a contact number and email address to use if they have questions, and will also be offered the option of taking the questionnaire via telephone.

Out of State Residents

DHHS will work with the State Health Departments and Cancer Registries to determine a process for reaching out to and including out of state residents in the investigation process.

Nationally

The case definition and karen.paddleford@dhhs.nh.gov email will be made available on the DHHS website for people to share with potential cases. DHHS will rely on community members to help us identify people who may have been connected with the area (e.g., lived, attended school or worked there) and have moved out of New Hampshire. We will not contact individuals outside of New Hampshire on the basis of information from the community, unless the family contacts the email address above and provides identification and medical confirmation of the diagnosis.

The template case outreach letter will inform individuals affected by RMS or PPB about: 1) the investigation underway in New Hampshire; 2) why they have been contacted; 3) the case definition for inclusion in our investigation (e.g., 28 cumulative days in the 10-town area); and 4) how to indicate their willingness to participate. Individuals willing to participate in the study will be asked to return a signed consent form. During the consent process individuals will be asked how they prefer to respond to the questionnaire.

3. Consent and Data Collection

By Phone

Epidemiologists at the State Health Department will be available to complete phone-based case questionnaire interviews for those indicating a preference for this. Prior to interviews, written consent will be obtained from participants.

By Mail

Paper copies of the questionnaire and informed consent form will be mailed to individuals as described above. Self-addressed stamped envelopes will be included with surveys to help facilitate their return to DHHS. Returned surveys will be entered into a database. The database will be saved on the shared drive in a folder with restricted access. If the survey is not returned within 2 weeks of mailing, up to three reminder phone calls will be made. At any stage, the family may decline to participate further, and additional reminder phone calls will not be made.

4. Analysis

The Chronic Disease Epidemiologist will perform a descriptive analysis on the survey data (e.g., numbers and frequency of responses by item).

5. Follow-Up

Results will be used to inform DHHS regarding whether to recommend further investigation be conducted. This recommendation would be made only if there is a strong enough suggestion between a common environmental or chemical cause and cases. Logistics for completing such a study would require further planning and decision-making to identify the lead agency. A published report with a summary of the case study process and any relevant findings will be posted on the DHHS website and shared in a subsequent community meeting. Release of information will be consistent with DHHS and HIPPA rules around protection of privacy. Study participants will be notified when results are shared publicly via mail or email.

References

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